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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	5

DATE MAILED: 06/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/841,744	DIMARTINO, JORGE F.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-43 is/are pending in the application.

4a) Of the above claim(s) 3,5,29 and 31-38 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,2,4,6-28,30 and 39-43 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U. S. C. 121:

Claims 1-43, drawn to a method of treating a disease associated with aberrant silencing of gene expression, comprising administering to a patient a DNA methylation inhibitor and a histone deacetylase inhibitor, and to a kit for treating a disease associated with aberrant silencing of gene expression, comprising a container that contains decitabine and a histone deacetylase inhibitor, classified in class 514, subclasses 11 and 449, and class 546, subclass 113.

Applicant is required to select one disease from claim 2, 3, 4 or 5. Each disease is considered patentably distinct because the diagnosis of each disease state is different, each disease can be treated with a different drug and has different outcome for the treatment. Applicant is also required to select one type of histone deacetylase inhibitor from claim 8 and claim 39, and one type of antineoplastic agent from claim 28. Each type of histone deacetylase inhibitor or each type of antineoplastic agent is considered patentably distinct because each type of compound has different chemical properties and produces different effects in the method of treatment. For example, the histone deacetylase inhibitor, n-butyrate inhibits histone deacetylase in a noncompetitive manner and induces a variety of biological phenomena such as differentiation and cell cycle arrest, while trichostatin A, a hydroxamic acid, causes potent and reversible inhibition of mammalian histone deacetylase at nanomolar concentration both *in vivo* and *in vitro*, and trapoxin, a cyclic tetrapeptide inhibits histone deacetylase irreversibly (see page

22429, right column in Kijima *et al.*, J. Biol. Chem. 268, 22429-22435 (1993)). Regarding various antineoplastic agents, anthracyclines, an antibiotic agent, interfere with the action of DNA topoisomerase II in the regions of transcriptional active DNA, which leads to DNA strand scissions (page 24, lines 18-20 of the specification), while the plant-derived agents such as vinca alkaloids generally act as antimitotic agents that bind to tubulin and inhibit mitosis (page 25, lines 10-18 of the specification).

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by the recognized divergent subject matter, and because Inventions require different searches but are not co-extensive, examination of these distinct inventions would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

During a telephone conversation with Shirley Chen on May 21, 2002 a provisional election was made with traverse to prosecute the invention of claims 1-43 with cancer as the elected disease, hydroxamic acid as the histone deacetylase inhibitor, and antibiotic agent as the antineoplastic agent. Upon reconsideration, other histone deacetylase inhibitors cited in claim 8 including cyclic peptide, benzamide, butyrate and depudecin will be examined. Affirmation of this election must be made by applicant in replying to this Office action. Claims 3, 5, 29 and 31-38 recite non-elected diseases and antineoplastic agents, thus they are withdrawn from further consideration by the examiner, see 37 CFR 1.142(b). Claims 1, 2, 4, 6-28, 30 and 39-43 are examined.

Claim Objections

2. Claim 4 is objected to because of the misspelling word "polycythermia".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 2, 4, 6-28, 30 and 39-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating metastatic colon cancer comprising administering a DNA methylation inhibitor decitabine and a histone deacetylase inhibitor such as trichostatin A or a butyrate, or along with an antibiotic agent, wherein the cancer associated differentiation-related gene-1 (Drg-1) is not expressed in metastatic colon cancer cells, as indicated in the prior art, does not reasonably provide enablement for a method for treating a disease associated with aberrant silencing of gene expression comprising administering a DNA methylation inhibitor and a histone deacetylase inhibitor, or along with an antibiotic agent; or a kit for treating a disease associated with aberrant silencing of gene expression comprising a container that contains decitabine and a histone deacetylase inhibitor of hydroxamic acid, cyclic peptide, benzamide, butyrate or depudecin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1, 2, 4, 6-28, 30 and 39-43 are directed to a method for treating a disease or a cancer associated with aberrant silencing of gene expression comprising administering a DNA methylation inhibitor and a histone deacetylase inhibitor (claims 1, 2, 4, 6-27), or along with an antibiotic agent (claims 28 and 30); or a kit for treating a disease associated with aberrant silencing of gene expression comprising a container that contains decitabine and a histone

deacetylase inhibitor of hydroxamic acid, cyclic peptide, benzamide, butyrate or depudecin (claims 39-43). The specification, however, only discloses cursory conclusions without data supporting the findings, which states that kits and methods for treating a disease such as cancer using a combination therapy which includes a DNA methylation inhibitor and a histone deacetylase inhibitor are provided, and the combination therapy triggers cancer cell death through reestablishment of intrinsic death mechanisms of cells such as growth arrest, differentiation and apoptosis through activation of genes selectively silenced in cancer cells (page 8, lines 8-18). There are no indicia that the present application enables the full scope in view of a method for treating a disease using a DNA methylation inhibitor and a histone deacetylase inhibitor as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses an unspecified variants regarding the diseases or cancers being treated, the associated genes silently expressed, the DNA methylation inhibitors and histone deacetylase inhibitors used, which are not adequately described or demonstrated in the specification.

(2). The absence of working examples:

There are no working examples indicating the claimed variants and the methods in association with the variants.

(3). The state of the prior art and relative skill of those in the art:

The prior art indicates the use of decitabine with a butyrate or trichostatin A to up-regulate the expression of Drg-1 in metastatic colon cancer cells and to treat the metastasis of colon cancer (Guan *et al.*, Cancer Research 60, 749-755 (February 2000); Cameron *et al.*, Nature Genetics 21, 103-107 (January 1999)). However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identities of the disease or cancer being treated, the associated genes silently expressed, the DNA methylation inhibitors and histone deacetylase inhibitors used in the combination therapy to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method for treating a disease or a cancer associated with aberrant silencing of gene expression comprising administering a DNA methylation inhibitor and a histone deacetylase inhibitor. However, the specification does not identify a specific disease or cancer being treated, the related gene being expressed in the combination therapy, and the effects of the agents used, the invention is highly unpredictable regarding the outcome of the treatment without identifying the type and the disease state of the cancer. For example, Nakayama *et al.* (Laboratory Investigation 80, 1789-1796 (December 2000)) teach three prostate cancer cell lines are treated with decitabine and trichostatin A, and re-expression of androgen receptor gene mRNA is detected in DU145 after the treatment, where DU145 cell lines are androgen-

independent cell lines and are from advanced metastatic prostate cancer; Cinar *et al.* (Cancer Research 61, 7310-7317, (October 2001)) teach androgen-repressed human prostate cancer cell line (ARCaP, a metastatic prostate cancer cell line) is transduced with wildtype human androgen receptor (hAR), and hAR-transduced ARCaP cells exhibit reduced growth invasion, and migratory behavior *in vitro* and tumor growth *in vivo*; However, Zhu *et al.* (Endocrinology 140, 5451-5454 (1999)) teach a nonsteroidal anti-inflammatory drug flufenamic acid (FA) inhibits the androgen receptor (AR) expression at mRNA and protein levels in LNCaP (an androgen-responsive human prostate cancer cell lines), and the inhibition of LNCaP growth by FA is due to its suppression of AR expression. Therefore, the references suggest that the benefits on regulation of the gene expression of AR in cancer treatment is not predictable if the disease state of the cancer cells is not identified.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method for treating a disease or a cancer associated with aberrant silencing of gene expression comprising administering a DNA methylation inhibitor and a histone deacetylase inhibitor. The specification indicates a combination therapy including a DNA methylation inhibitor and a histone deacetylase inhibitor can be used for treating a disease such as cancer. However, there is no working example indicating the treatment of a specific disease or cancer using an identified DNA methylation inhibitor and an identified histone deacetylase inhibitor. The specification has not demonstrated a specific disease or cancer being treated, the re-expression of the related gene in the combination therapy, and the effects of the agents used. Since the specification fails to provide sufficient guidance on the identities of

cancer being treated, the related gene being monitored, and the specific DNA methylation inhibitor and histone deacetylase inhibitor used in the combination therapy, it is necessary to carry out further experimentation to assess the effects of the agents in treating the disease such as cancer.

(6). Nature of the Invention

The scope of the claims encompass treating a disease or a cancer associated with aberrant silencing of gene expression comprising administering a DNA methylation inhibitor and a histone deacetylase inhibitor, but the specification does not identify the disease being treated, the related gene being monitored, and the specific DNA methylation inhibitor and histone deacetylase inhibitor used in the combination therapy. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed variants, the art is unpredictable regarding the variants, and the guidance and the teaching in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of various DNA methylation inhibitors and histone deacetylase inhibitors in the method of treating a disease such as cancer.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 2, 4, 6-28 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 4, 6-28 and 30 are indefinite because the claim lacks essential steps in the method of treating a disease associated with aberrant silencing of gene expression. The omitted steps are the method of administration and the outcome of the treatment. Claims 2, 4, 6-28 and 30 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

5. Claims 1, 2, 4, 6-28, 30 and 39-43 are indefinite because of the use of the term "a disease associated with aberrant silencing of gene expression". The term "a disease associated with aberrant silencing of gene expression" renders the claim indefinite, it is not clear which disease is being treated, and which gene is associated with the disease, where the gene is transcriptionally silenced. Claims 2, 4, 6-28, 30 and 40-43 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

6. Claims 2, 4 and 28 are indefinite because the claim contains non-elected inventions. For example, claim 2 contains restenosis; claim 4 contains a disease, which is not cancer, e.g., gallstone.

7. Claim 6 is indefinite because of the use of the term "cytidine analog". The term "cytidine analog" renders the claim indefinite, it is not clear what compound the cytidine analog is, and how different the analog is as compared to the parent compound.

8. Claims 10, 11, 41 and 42 are indefinite because of the use of the term "FR901228" or "MS-27-275". The term "FR901228" or "MS-27-275" renders the claim indefinite, it is not clear what kind of compound is as to "FR901228" or "MS-27-275". A chemical name should be indicated at the first occurrence.

9. Claim 28 is indefinite because of the use of the term "one or more". The term "one or more" renders the claim indefinite, it is not clear how many antineoplastic agents are administered as to "one or more".

Claim Rejections - 35 USC § 102&103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1, 2, 4, 6-8 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Guan *et al.* (Cancer Research 60, 749-755 (February 2000)).

Guan *et al.* teach the use of a histone deacetylase inhibitor such as trichostatin A, or a combination of tributyrin (a prodrug of butyrate) and decitabine to up-regulate the expression of Drg-1 (a putative metastatic suppressor gene in human colon cancer) in metastatic colon cancer cells (page 753; Fig. 6; claims 6-8), wherein Drg-1 is not expressed. Overexpression of Drg-1 in metastatic colon cells reduced *in vitro* invasion through Matrigel and suppressed *in vivo* liver metastases in nude mice (page 753; Fig. 7 and Table 1). The reference also suggests the use of

histone deacetylase inhibitor to induce the expression of Drg-1 for treating metastasis of colon cancer cells (page 755, second paragraph), thus it is obvious to use the combination of a butyrate and decitabine to treat the metastasis of colon cancer in patient because of the synergistic effect of the two agents (claims 1, 2, 4 and 12).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guan *et al.* (Cancer Research 60, 749-755 (February 2000)) in view of Cameron *et al.* (Nature Genetics 21, 103-107 (January 1999)).

Guan *et al.* teach the use of a histone deacetylase inhibitor such as trichostatin A, or a combination of tributyrin (a prodrug of butyrate) and decitabine to up-regulate the expression of Drg-1 (a putative metastatic suppressor gene in human colon cancer) in metastatic colon cancer cells (page 753; Fig. 6), wherein Drg-1 is not expressed. Overexpression of Drg-1 in metastatic colon cells reduced *in vitro* invasion through Matrigel and suppressed *in vivo* liver metastases in nude mice (page 753; Fig. 7 and Table 1). The reference suggests the use of a butyrate and decitabine to treat the metastasis of colon cancer in patient. However, Guan *et al.* do not disclose the synergistic effect of trichostatin A and decitabine. Cameron *et al.* teach the synergistic effect of trichostatin A and decitabine in reexpression of genes such as MLH1 and p16 in cancer cells (page 104). At the time of invention was made, it would have been obvious to one of ordinary

skill in the art to use decitabine and trichostatin A instead of decitabine and butyrate as indicated by Cameron *et al.* for treating metastastic colon cancer taught by Guan *et al.* because the combination therapy using a different histone deacetylase inhibitor would provide an alternative agent for treating colon cancer. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

12. Claims 28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guan *et al.* in view of Boyd *et al.* (U. S. Patent 5,283,383).

Guan *et al.* teach the use of a histone deacetylase inhibitor such as trichostatin A, or a combination of tributyrin (a prodrug of butyrate) and decitabine to up-regulate the expression of Drg-1 (a putative metastatic suppressor gene in human colon cancer) in metastatic colon cancer cells (page 753; Fig. 6), wherein Drg-1 is not expressed. Overexpression of Drg-1 in metastatic colon cells reduced *in vitro* invasion through Matrigel and suppressed *in vivo* liver metastases in nude mice (page 753; Fig. 7 and Table 1). The reference suggests the use of a butyrate and decitabine to treat the metastasis of colon cancer in patient. However, Guan *et al.* fail to disclose the inclusion of an antineoplastic agent in the treatment. Boyd *et al.* disclose the method of treating cancer using the compound of 6(R)-bromo, 3(S)-bromomethyl-7-methyl-2,3,7-trichloro-1-octene can be made more effectively by administering other anticancer compounds such as doxorubicin (column 5, line 52-column 6, line 3). Therefore, at the time the invention was made, it would have been obvious to a person of ordinary skill in the art to use decitabine and a butyrate as taught by Guan *et al.* in conjunction with doxorubicin as indicated by Boyd *et al.* for treating cancer because the use of decitabine and a butyrate in combination with doxorubicin can

act synergistically in the treatment of cancer. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Conclusion

13. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

June 8, 2002

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER